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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,634	10/27/2003	Jun Tan	12062.105020	2636

65989 7590 04/29/2008

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/694,634	TAN ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 93-104, 107, and 110-121* is/are pending in the application.

4a) Of the above claim(s) *95,98 and 100-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,93,94,96,97,99,107 and 110-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/08/2008 has been entered.

Election/Restrictions

2. A restriction requirement between the different inventions and species recited in original claims 1-92 was mailed on 04/24/2006. In the reply filed on 09/29/2006 Applicant elected without traverse the invention of Group I (claims 1-20) drawn to a method of screening for compounds which modulate the CD40L/CD40R signaling pathway in an animal. In the same reply Applicant elected the species of central nervous system cells, tumor necrosis factor as marker, a test compound which binds to CD40L, and of animal suffering from neuronal inflammation.

In the request for continued examination filed on 02/08/2008, Applicant cancelled the claims directed to the elected species of tumor necrosis factor as a marker and amended the claims to recite that the marker is β-amyloid precursor protein (β-APP).

Claims 2-92, 105, 106, 108, and 109 have been cancelled. Claims 95, 98, and 100-104 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b)

as being drawn to a nonelected species of compounds to be screened. Claim 1 has been amended. Claim 121 is new.

Claims 1, 93, 94, 96, 97, 99, 107, and 110-121 are under examination.

2. All rejections pertaining to claims 3, 4, 108, and 109 are moot because Applicant cancelled the claims in the response filed on 02/08/2008.

All previous rejections are withdrawn in response to Applicant's amendments to the claims filed on 02/08/2008.

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 110-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 step (ii) recites the limitation "neuronal cells" in step (i). There is insufficient antecedent basis for this limitation in step(i) of claim 1.

Claims 110-120 recite the limitation "neuronal cells" in claim 1. There is insufficient antecedent basis for this limitation in claim 1.

Claim Rejections - 35 USC § 112, first paragraph, new matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 93, 94, 96, 97, 99, 107, and 112-121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 2, 8-9, 11, 14-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claim to delete reference to neuronal cells and include the term "cells that express CD40R and β-amyloid precursor protein" is considered new matter. By this amendment, Applicant broadened the scope of the claims from neuronal cell to any cell expressing CD40 and β-APP. Such a broad genus is not supported by the instant specification because, with the exception of neuronal cells and microglia, the specification does not teach using cells which expresses both CD40 and β-APP (see MPEP 2163.05 [R-2]).

Applicant points to p.1, paragraph 0004, p. 2-3, paragraph 0006, p. 7, paragraph 0016, p. 13-14, paragraph 0035, and p. 31-32, paragraph 0093 for support. It is noted that the indicated paragraphs 0004, 0006, 0016, and 0035 refer to the connection

between β-APP processing and Alzheimer's disease and to the use of β-APP as a marker in the claimed assay. Paragraph 0093 does recite the neuroblastoma cell line N2a which expresses CD40 and overexpresses the wild type APP-751 transgene. It is noted that the art teaches that only microglia and neuronal cells naturally express both CD40 and β-APP. The specification discloses that various cells could be used in the assay, including transgenic cells (p. 13, paragraph 0034). While the use of cells expressing CD40 (including transgenic cells overexpressing CD40) is inherent to a method of screening for agents which modulate the CD40L/CD40 signaling pathway, the use of cells expressing β-APP or transgenic cells overexpressing β-APP is not, since a wide range of markers could be used to monitor the assay, as disclosed by the instant specification (see the specification, p. 7, paragraph 0016, p. 13 and 14, paragraph 0034). The original claims recited a method using neuronal cells; the amended claims recite a method using cells expressing both CD40 and β-APP, i.e., as noted above, Applicant broadened the scope of the claims to encompass any cell which expresses both CD40 and β-APP. Such a broad genus is not supported by the specification, for the reasons indicated above.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or

terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 93, 94, 96, 97, 99, 100, 107, and 110-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (Science, 1999, 286: 2352-2355, of record), in view of each Gehrmann et al. (Glia, 1995, 15: 141-151), Gerritse et al. (Proc Natl Acad Sci USA, 1996, 93: 2499-2504, of record), LeBlanc et al. (J Neurochem, 1996, 66: 2300-2310), and Tan et al. (EMBO J, February 2002, 21: 643-652, of record).

** For examination purposes, claims 112-120 dependent from claim 1 are interpreted as being directed to cells expressing both CD40 and βAPP, as recited in claim 1. It is noted that the specification teaches that neuronal and the N2a cells

express CD40 and βAPP, and therefore, they are encompassed the genus recited in claim 1.

Tan et al. teach a method for testing the ability of monoclonal antibodies directed against CD40R to interfere with the CD40L/CD40R signaling pathway in microglia, the method comprising: (i) contacting a first sample of microglial cells with CD40L and measuring the level of the produced TNF-α, (ii) contacting a second sample of activated microglial cells with CD40L in the presence of an anti-CD40R antibody, and measuring the level of the produced TNF-α, and (iii) comparing the level of TNF-α in the first sample with the level of TNF-α in the second sample (claims 1, 93, and 94); the microglia could be derived from transgenic animals overexpressing APP which animals are afflicted with Alzheimer's disease (claims 112, 113, and 116-120) (p. 2353, columns 1 and 2 ; Fig. 4). Tan et al. teach that CD40L binding to the CVD40R on microglia activates these cells and that activated microglia secrete increased amounts of TNF-α; TNF-α level can be used as a marker to determine whether the anti-CD40R antibodies are able to inhibit CD40L/CD40R signaling pathway (p. 2353, columns 1 and 2, p. 2354, column 1). With respect to the limitation of the cells expressing βAPP (claim 1), this is an inherent property of microglia (see LeBlanc et al., Abstract, p. 2302, column 2, p. 2303, column 2). Therefore, Tan et al. teach using cells expressing both CD40 and βAPP (claim 1).

Tan et al. do not teach using the amount of βAPP or fragment thereof as a marker (claim 1). However, the prior art teaches that, similar to TNF-α, βAPP expression is increased in activated microglia. For example, Gehrmann et al., teach

that activated microglia in patients affected with multiple sclerosis (MS) exhibit enhanced βAPP levels and that βAPP detection could be a sensitive marker for MS progression (Abstract). Furthermore, Gerritse et al. teach that activated microglia bearing CD40R on their surface are involved in MS progression (Abstract, p. 2499, column 2, second full paragraph, p. 2501, column 2, p. 2502, column 2, p. 2503, columns 1 and 2, p. 2504, column 1). Based on these teachings of CD40L/CD40R signaling pathway leading to Ms and of βAPP level as a marker for MS progression, one of skill in the art would know that activation of microglia by the CD40L/CD40R signaling pathway correlates with increased βAPP expression. It would have been obvious to one of skill in the art, at the time the invention was made, to substitute the TNF-α of Tan et al. with the βAPP of Gehrmann et al. to achieve the predictable result of assessing the ability of anti-CD40R antibodies to inhibit microglial activation in response to CD40L treatment.

With respect to the limitation testing agents being agents capable of binding CD40L (claims 94, 96, and 107), Gerritse et al. teach the advantage of screening for compounds that target CD40L; Gerritse et al. teach that CD40L has advantages over the constitutively and widely expressed CD40R as a target for intervention because its transient expression is restricted to $CD4^+$ T cells, which allows targeting of only those T cells actively participating in the response, without affecting the population of T cells at large (p. 2504, column 1). Based on these teachings, one of skill in the art would have been motivated to modify the method of Tan et al. by screening for antibodies that interfere with the CD40R/CD40L signaling pathway by binding to CD40L and would

have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of such methods to identify compounds with the ability of modulating the CD40L/CD40R signaling pathway. It is noted that by doing such, one of skill in the art would have necessarily identified antibodies that would decrease CD40L trimerization (claim 96).

With respect to the limitation of the marker being β-amyloid and of the antibody reducing the amount of β-amyloid (Aβ) levels relative to the control (claims 97, 99, and 121), it is noted that the art teaches that microglia process βAPP to yield Aβ (see LeBlanc et al., p. 2303, column 2). Therefore the antibody used in the method of Tan et al., Gehrmann et al., and Gerritse et al. necessarily reduces Aβ relative to the control.

Tan et al., Gehrmann et al., and Gerritse et al. do not teach using neuronal cells or the neuroblastoma N2a cells (claims 110 and 111). However, it is noted that the claims are directed to an *in vitro* method of screening for compounds that inhibit CD40L/CD40R signaling pathway by using cells expressing CD40R and βAPP; therefore, one of skill in the art would have known that the use of any cell expressing CD40 and βAPP would have yielded predictable results, i.e., identification of compounds that inhibit CD40L/CD40R signaling pathway. Applicant did not provide any evidence that the specific use of neuronal or N2a cells would result in unexpected results. Just because Applicant uses another cell type does not render the claims unobvious over the prior art. Moreover, it is noted that the prior the prior art teaches that neuronal cells express CD40R and βAPP (see Tan et al., EMBO J, Abstract, p. 644, columns 1 and 2, p. 645, column 2; LeBlanc et al., Abstract, p. 2303, column 2).

One of skill in the art would have known that the substitution of one cell for another cell would render the claimed results and would have known that neuronal or N2a cells could also be successfully employed in the claimed screening assay.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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